

WHAT IS CLAIMED IS:

1. An isolated antibody comprising an Fc region and three or more antigen binding sites amino-terminal to the Fc region.

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2. The antibody of claim 1 comprising four antigen binding sites.

3. The antibody of claim 1 comprising five or more antigen binding sites.

10 4. The antibody of claim 1 comprising a polypeptide chain, wherein the polypeptide chain comprises two or more variable domains.

5. The antibody of claim 4 wherein the polypeptide chain comprises $VD1-(X1)_n-VD2-(X2)_n-Fc$, wherein VD1 is a first variable domain, VD2 is a second variable domain, Fc is one polypeptide chain of an Fc region, X1 and X2 represent an amino acid or polypeptide, and n is 0 or 1.

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6. The antibody of claim 5 comprising two or more polypeptide chains, each comprising $VD1-(X1)_n-VD2-(X2)_n-Fc$.

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7. The antibody of claim 1 comprising at least one polypeptide chain with the formula:

- (a) VH-CH1-flexible linker-VH-CH1-Fc region chain; or
- (b) VH-CH1-VH-CH1-Fc region chain.

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8. The antibody of claim 1 comprising at least two light chain variable domain polypeptides.

9. The antibody of claim 8 wherein the light chain variable domain polypeptides further comprise a CL domain.

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10. The antibody of claim 1 comprising a polypeptide chain, wherein the polypeptide chain comprises Fd-flexible linker-Fd.

11. The antibody of claim 10 wherein the flexible linker comprises a peptide selected from the group consisting of gly-ser, gly-ser-gly-ser (SEQ ID NO:10), ala-ser, and gly-gly-gly-ser (SEQ ID NO:11).

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12. The antibody of claim 1 which is internalized faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind.

13. The antibody of claim 1 which is an agonist antibody.

14. The antibody of claim 1 which induces apoptosis.
15. The antibody of claim 1 wherein the three or more antigen binding sites all bind the same antigen.
16. The antibody of claim 1 wherein the three or more antigen binding sites bind two or more different antigens.
17. The antibody of claim 1 which binds a cell surface protein expressed by tumor cells.
18. The antibody of claim 17 wherein the cell surface protein is selected from the group consisting of the Epidermal Growth Factor Receptor (EGFR), HER2 receptor, HER3 receptor, HER4 receptor and DcR3 receptor.
19. The antibody of claim 17 wherein the cell surface protein is HER2 receptor.
20. The antibody of claim 1 which binds a cell surface protein overexpressed by tumor cells.
21. The antibody of claim 1 which binds a receptor in the Tumor Necrosis Factor (TNF) receptor superfamily.
22. The antibody of claim 21 wherein the TNF receptor is an Apo2L receptor.
23. The antibody of claim 22 wherein the Apo2L receptor is selected from the group consisting of DR4, DR5, DcR1 and DcR2.
24. The antibody of claim 22 wherein the Apo2L receptor is DR4 or DR5.
25. The antibody of claim 21 which is an agonist antibody.
26. The antibody of claim 21 which induces apoptosis.
27. The antibody of claim 1 which binds a B cell surface antigen.
28. The antibody of claim 27 wherein the B cell surface antigen is selected from the group consisting of CD19, CD20, CD22 and CD40.
29. The antibody of claim 27 wherein the B cell surface antigen is CD20.

30. An immunoconjugate comprising the antibody of claim 1 conjugated with a cytotoxic agent.
31. The immunoconjugate of claim 30 wherein the cytotoxic agent is active in killing cells once internalized.
32. The immunoconjugate of claim 30 wherein the cytotoxic agent is selected from the group consisting of a radioactive isotope, a maytansinoid and a calecheamicin.
33. An isolated antibody comprising three or more antigen binding sites, wherein the antibody is capable of binding a receptor in the Tumor Necrosis Factor (TNF) receptor superfamily.
34. The antibody of claim 33 which is not a native sequence IgM or IgA antibody.
35. The antibody of claim 33 which has only one Fc region or lacks an Fc region.
36. The antibody of claim 33 which comprises a polypeptide chain, wherein the polypeptide chain comprises two or more variable domains.
37. The antibody of claim 33 which comprises four antigen binding sites each capable of binding the TNF receptor.
38. The antibody of claim 33 wherein the TNF receptor is an Apo2L receptor.
39. The antibody of claim 38 wherein the Apo2L receptor is selected from the group consisting of DR4, DR5, DcR1 and DcR2.
40. The antibody of claim 38 wherein the Apo2L receptor is DR4 or DR5.
41. The antibody of claim 33 which is an agonist antibody.
42. The antibody of claim 33 which induces apoptosis.
43. An isolated antibody comprising at least three antigen binding sites, wherein the antibody is capable of binding an ErbB receptor.
44. The antibody of claim 43 which is not a native sequence IgM or IgA antibody.

45. The antibody of claim 43 which has only one Fc region or lacks an Fc region.
46. The antibody of claim 43 which comprises a polypeptide chain, wherein the polypeptide chain comprises two or more variable domains.
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47. The antibody of claim 43 which comprises four antigen binding sites each capable of binding the ErbB receptor.
48. The antibody of claim 43 wherein the ErbB receptor is selected from the group consisting of
10 Epidermal Growth Factor Receptor (EGFR), HER2 receptor, HER3 receptor and HER4 receptor.
49. The antibody of claim 43 where the ErbB receptor is HER2 receptor.
50. An isolated antibody comprising at least three antigen binding sites, wherein the antibody is capable of binding a B cell surface antigen.
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51. The antibody of claim 50 which is not a native sequence IgM or IgA antibody.
52. The antibody of claim 50 which has only one Fc region or lacks an Fc region.
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53. The antibody of claim 50 which comprises a polypeptide chain, wherein the polypeptide chain comprises two or more variable domains.
54. The antibody of claim 50 which comprises four antigen binding sites each capable of the B cell surface antigen.
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55. The antibody of claim 50 wherein the B cell surface antigen is selected from the group consisting of CD19, CD20, CD22 and CD40.
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56. An isolated antibody comprising at least three antigen binding sites, wherein the antibody is capable of binding an antigen which is overexpressed by cancer cells.
57. A polypeptide chain comprising:
 - (a) VH-CH1-flexible linker-VH-CH1-dimerization domain; or
 - 35 (b) VH-CH1-VH-CH1-dimerization domain.
58. An isolated antibody comprising the polypeptide chain of claim 57.

59. The antibody of claim 58 further comprising two or more light chain variable domain polypeptides.
60. The antibody of claim 59 wherein the light chain variable domain polypeptides comprise VL-CL.
- 5 61. An isolated antibody comprising a dimerization domain and three or more antigen binding sites amino-terminal thereto
62. The antibody of claim 61 wherein the dimerization domain is selected from the group consisting of a hinge region, an Fc region, a CH3 domain, and a CH4 domain.
- 10 63. The antibody of claim 62 wherein the dimerization domain is a hinge region.
64. The antibody of claim 63 wherein the dimerization domain further comprises a leucine zipper.
- 15 65. The antibody of claim 63 comprising a polypeptide chain comprising the formula:
(a) VH-CH1-flexible linker-VH-CH1-hinge region; or
(b) VH-CH1-VH-CH1-hinge region.
- 20 66. A polypeptide chain comprising three or more heavy chain or light chain variable domains, wherein each of the variable domains is able to combine with three or more light chain or heavy chain variable domain polypeptides to form three or more antigen binding sites, each directed against the same antigen.
- 25 67. The polypeptide chain of claim 66 which comprises three heavy chain variable domains which are able to combine with three light chain variable domain polypeptides to form three antigen binding sites directed against the same antigen.
68. The polypeptide chain of claim 66 which comprises four heavy chain variable domains which are able to combine with four light chain variable domain polypeptides to form four antigen binding sites directed against the same antigen.
- 30 69. The polypeptide chain of claim 66 wherein the antigen is a receptor in the Tumor Necrosis Factor (TNF) receptor superfamily.
- 35 70. The polypeptide chain of claim 66 wherein the antigen is a B cell surface antigen.
71. The polypeptide chain of claim 66 wherein the antigen is an ErbB receptor.

72. The polypeptide chain of claim 66 wherein the antigen is a cell surface protein expressed by tumor cells.
73. A polypeptide chain comprising the formula:
- (a) VL-CL-flexible linker-VL-CL-flexible linker-VL-CL;
 - (b) VH-CH1-flexible linker-VH-CH1-flexible linker-VH-CH1;
 - (c) (VL-CL)_n, wherein n is three or more; or
 - (d) (VH-CH1)_n, wherein n is three or more.
74. The polypeptide chain of claim 67 comprising the formula:
- (a) VH-CH1-flexible linker-VH-CH1-flexible linker-VH-CH1;
 - (b) VH-CH1-flexible linker-VH-CH1-flexible linker-VH-CH1-flexible linker-VH-CH1; or
 - (c) (VH-CH1)_n, wherein n is three or four.
75. An isolated antibody comprising the polypeptide chain of claim 66.
76. The isolated antibody of claim 75 further comprising the three or more light chain or heavy chain variable domain polypeptides.
77. The isolated antibody of claim 76 comprising three or more light chain variable domain polypeptides, each comprising VL-CL.
78. The isolated antibody of claim 77 comprising four light chain variable domain polypeptides, each comprising VL-CL.
79. A polypeptide chain comprising:
- (a) VL-CL-flexible linker-VL-CL-dimerization domain;
 - (b) VL-CL-VL-CL-dimerization domain.
80. An immunoconjugate comprising the antibody of claim 75 conjugated with a cytotoxic agent.
81. Isolated nucleic acid encoding the antibody of claim 1, the polypeptide chain of claim 57 or the polypeptide chain of claim 66.
82. A vector comprising the nucleic acid of claim 81.
83. A host cell comprising the nucleic acid of claim 81.

84. A process of producing an antibody or polypeptide chain comprising culturing the host cell of claim 83 so that the nucleic acid is expressed.

5 85. The process of claim 84 further comprising recovering the antibody or polypeptide chain from the host cell culture.

86. The process of claim 85 wherein the antibody or polypeptide chain is recovered from the host cell culture medium.

10 87. A method for treating a disorder in a mammal comprising administering to the mammal a therapeutically effective amount of the antibody of claim 1.

88. The method of claim 87 wherein the disorder is cancer.

15 89. The method of claim 87 further comprising administering a therapeutically effective amount of a cytotoxic agent to the mammal.

20 90. A method of inducing apoptosis of a cancer cell comprising exposing the cell to the antibody of claim 33.

25 91. A method of killing a B cell comprising exposing the B cell to the antibody of claim 50.

92. A method of killing a cell which expresses an ErbB receptor comprising exposing the cell to the antibody of claim 43.

93. The method of claim 92 wherein the cell is a cancer cell which overexpresses an ErbB receptor.